# Supplementary Online Content

Shao Z, Pang D, Yang H, et al. Efficacy, safety, and tolerability of pertuzumab, trastuzumab, and docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia: the PEONY phase 3 randomized clinical trial. *JAMA Oncol.* Published online October 24, 2019. doi:10.1001/jamaoncol.2019.3692



This supplementary material has been provided by the authors to give readers additional information about their work.

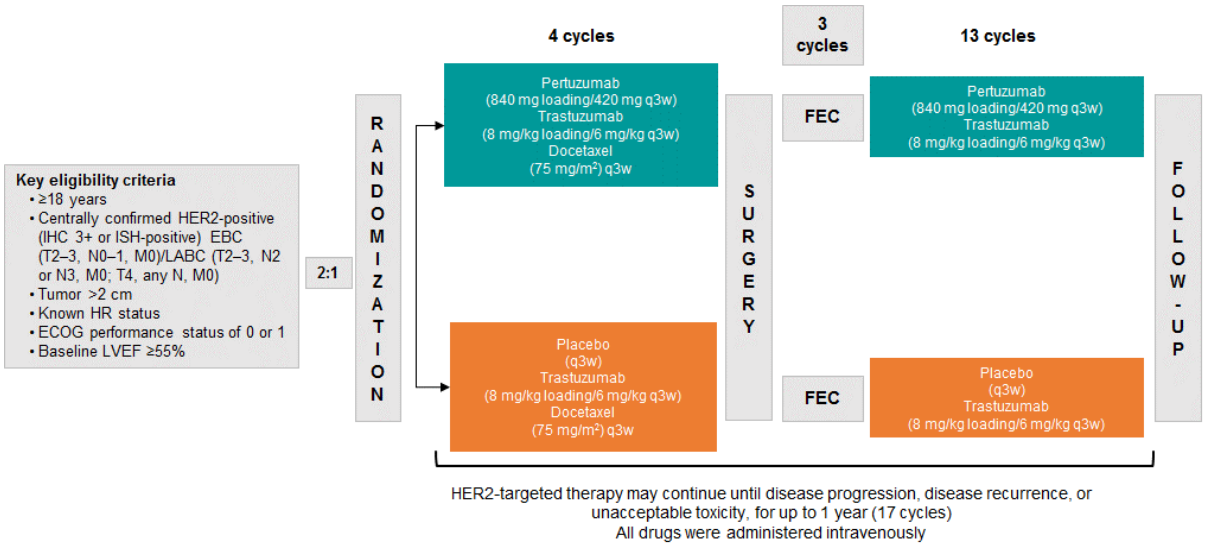
**eAppendix 1.** Investigators

| Principal Investigator | Center | Number of patients |
|---|---|---|
| Shao, Zhimin | Fudan University Shanghai Cancer Center, Shanghai, China | 81 |
| Pang, Da | Harbin Medical University Cancer Hospital, Harbin, China | 34 |
| Yang, Hongjian | Zhejiang Cancer Hospital, Hangzhou, China | 33 |
| Li, Wei | The First Hospital of Jilin University, Changchun, China | 18 |
| Wang, Shusen | Sun Yat-sen University Cancer Center, Guangzhou, China | 18 |
| Cui, Shude | Henan Cancer Hospital, Zhengzhou, China | 16 |
| Liao, Ning | Guangdong General Hospital, Guangzhou, China | 15 |
| Wang, Yongsheng | Shandong Cancer Hospital, Jinan, China | 14 |
| Wang, Chuan | Fujian Medical University Union Hospital, Fuzhou, China | 13 |
| Chang, Yuan-Ching | Mackay Memorial Hospital, Taipei City, Taiwan | 12 |
| Wang, Hweichung | China Medical University Hospital, Taichung City, Taiwan | 12 |
| Kang, Seok Yun | Ajou University School of Medicine, Suwon, Republic of Korea | 12 |
| Seo, Jae Hong | Korea University Guro Hospital, Seoul, Republic of Korea | 11 |
| Shen, Kunwei | Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China | 8 |
| Laohawiriyakamol, Suphawat | Songklanagarind Hospital, Department of Surgery, Songkhla, Thailand | 6 |
| Jiang, Zefei | The Affiliated Hospital of Military Medical Sciences (The 307$^{th}$ Hospital of Chinese People's Liberation Army), Beijing, China | 5 |
| Chao, Tsu-Yi | Taipei Medical University Shuang Ho Hospital, Taipei, Taiwan | 4 |
| Vachirodom, Damnern | Srinagarind Hospital, Khon Kaen University; Surgery, Khon Kaen, Thailand | 4 |
| Cheng, Ying | Jilin Cancer Hospital, Changchun, China | 4 |
| Chao, Tsu-Yi | Taipei Medical University Hospital, Taipei, Taiwan | 3 |
| Upachar, Chutima | Bhumibol Adulyadej Hospital; Medicine, Bangkok, Thailand | 2 |
| Chae, Yee Soo | Kyungpook National University Medical Center, Daegu, Republic of Korea | 2 |
| Zha, Xiaoming | Jiangsu Province Hospital, Nanjing, China | 2 |

**eAppendix 2.** Clinical Response Measurement

Clinical response rates, including the proportions of patients with a complete response, partial response, stable disease, or progressive disease, were determined by the investigator during Cycles 1−4 (i.e., prior to surgery) on the basis of RECIST v1.1. Objective response rate was defined as the proportion of patients achieving a complete response or partial response as the best tumor response during the neoadjuvant period. No confirmation was required for objective response. Only patients with measurable disease at baseline were included in the analysis.

**eFigure.** Study Design




**Outcomes**

- Primary endpoint: tpCR rate (defined as absence of any residual invasive cancer in the breast and lymph nodes [ypT0/is, ypN0]) assessed by IRC when patients completed surgery with a tpCR assessment.
- Secondary efficacy endpoints: tpCR rate as assessed by the local pathologist, bpCR rate (defined as absence of any residual invasive cancer in the breast [ypT0/is]) as assessed by IRC and by the local pathologist, clinical response rates during Cycles 1–4, event-free survival, disease-free survival, and overall survival.
- Safety and tolerability was also assessed. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.

**Assessments**

- Tumors were assessed at baseline, at each cycle of neoadjuvant treatment, and before surgery.
- tpCR was assessed by the local pathologist and separately by the IRC. Extensive IRC training was provided to the local pathologists, and examination of specimens followed the guidelines of the College of American Pathologists.
- During the adjuvant treatment period, patients continue to be assessed for recurrence at least every 3 months (ie, cycle 9, cycle 13, cycle 17, and at the study completion or early termination visit).

Green boxes represent the pertuzumab arm. Orange boxes represent the placebo arm.
Randomization was via a permuted block procedure and an interactive voice or web response system (IxRS; PAREXEL Informatics; Waltham, MA, USA). Investigators and patients were blinded to the treatment assignment. All other individuals who were directly involved in this study remained blinded to the treatment assignment until completion of the primary analysis. Patient treatment assignment will not be unblinded until after the final analysis.
bpCR, pathologic complete response in the breast; ECOG, Eastern Cooperative Oncology Group; EBC, early breast cancer; FEC, fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; IRC, independent review committee; ISH, in situ hybridization; LABC, locally advanced breast cancer; LVEF, left ventricular ejection fraction; q3w, every 3 weeks; tpCR, total pathologic complete response.

**eTable 1.** Baseline Demographics and Characteristics (ITT Population)

| Demographic/Characteristic | Pertuzumab, Trastuzumab, and Docetaxel (n = 219) | Placebo, Trastuzumab, and Docetaxel (n = 110) | *P* Value |
|---|---|---|---|
| Median age, years (range) | 49 (24–72) | 49 (27–70) | .32[a] |
| Age group, no. (%) | | | .48[b] |
| <40 years | 40 (18.3) | 18 (16.4) | |
| 40–49 years | 75 (34.2) | 40 (36.4) | |
| 50–64 years | 96 (43.8) | 44 (40.0) | |
| ≥65 years | 8 (3.7) | 8 (7.3) | |
| Region, no. (%) | | | .53[b] |
| Mainland China | 175 (79.9) | 86 (78.2) | |
| Taiwan | 18 (8.2) | 13 (11.8) | |
| Other | 26 (11.9) | 11 (10.0) | |
| ECOG performance status, no. (%) | | | .53[b] |
| 0 | 198 (90.4) | 97 (88.2) | |
| 1 | 21 (9.6) | 13 (11.8) | |
| Hormone receptor status (IxRS), no. (%) | | | .85[b] |
| ER- and PgR-negative | 105 (47.9) | 54 (49.1) | |
| ER- and/or PgR-positive | 114 (52.1) | 56 (50.9) | |
| Menopausal status, no. (%) | | | .84[b] |
| Premenopausal | 132 (60.3) | 65 (59.1) | |
| Postmenopausal | 87 (39.7) | 45 (40.9) | |
| Disease status (IxRS), no. (%) | | | .91[b] |
| Early | 152 (69.4) | 77 (70.0) | |
| Locally advanced | 67 (30.6) | 33 (30.0) | |
| Primary tumor stage, no. (%) | | | .47[b] |
| T2 | 155 (70.8) | 71 (64.5) | |
| T3 | 45 (20.5) | 29 (26.4) | |
| T4 | 19 (8.7) | 10 (9.1) | |
| Lymph node status, no. (%) | | | .12[b] |
| Positive | 160 (73.1) | 89 (80.9) | |
| Negative | 59 (26.9) | 21 (19.1) | |
| Histologic subtype, no. (%)[c] | | | .49[b] |
| Ductal | 203 (92.7) | 103 (93.6) | |
| Lobular | 4 (1.8) | 1 (0.9) | |
| Comedo | 0 | 1 (0.9) | |
| Other/comedo | 15 (6.8) | 8 (7.3) | |
| HER2 IHC score, no. (%) | | | .09[b] |
| 1+ | 2 (0.9) | 0 | |

| | | | |
|---|---|---|---|
| 2+ | 65 (29.7) | 22 (20.0) | |
| 3+ | 152 (69.4) | 88 (80.0) | |

All patients were female and of Asian race. [a] T-test. [b] Chi-square test. [c] More than one subtype could be selected.
ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITT, intention-to-treat; IxRS, interactive voice or web response system; PgR, progesterone receptor.

**eTable 2.** Exposure to Study Medication (Safety Population)

| Exposure | Pertuzumab, Trastuzumab, and Docetaxel (n = 218) | Placebo, Trastuzumab, and Docetaxel (n = 110) |
|---|---|---|
| **Pertuzumab/placebo** | | |
| Treatment duration, weeks | | |
| Mean (SD) | 12.0 (1.2) | 12.0 (0.7) |
| Median | 12.0 | 12.0 |
| Range | 3–16 | 6–14 |
| Number of cycles | | |
| Mean (SD) | 3.9 (0.4) | 4.0 (0.2) |
| Median | 4.0 | 4.0 |
| Range | 1–4 | 2–4 |
| Number of cycles, no. of patients (%) | | |
| 1 | 3 (1.4) | 0 |
| 2 | 1 (0.5) | 1 (0.9) |
| 3 | 0 | 1 (0.9) |
| 4 | 214 (98.2) | 108 (98.2) |
| Cumulative dose, mg | | |
| Mean (SD) | 2082.7 (16.9) | 2084.9 (96.6) |
| Median | 2100.0 | 2100.0 |
| Range | 840–2520 | 1260–2100 |
| Number of infusion modifications, no. of patients (%) | | |
| 0 | 211 (96.8) | 110 (100) |
| 1 | 7 (3.2) | 0 |
| Number of infusion modifications due to an adverse event, no. of patients (%) | | |
| 0 | 212 (97.2) | 110 (100) |
| 1 | 6 (2.8) | 0 |
| **Trastuzumab** | | |
| Treatment duration, weeks | | |
| Mean (SD) | 12.0 (1.2) | 12.0 (0.7) |
| Median | 12.0 | 12.0 |
| Range | 3–16 | 6–14 |
| Number of cycles | | |
| Mean (SD) | 3.9 (0.4) | 4.0 (0.2) |
| Median | 4.0 | 4.0 |
| Range | 1–4 | 2–4 |
| Number of cycles, no. of patients (%) | | |
| 1 | 3 (1.4) | 0 |
| 2 | 1 (0.5) | 1 (0.9) |
| 3 | 0 | 1 (0.9) |
| 4 | 214 (98.2) | 108 (98.2) |
| Cumulative dose, mg | | |
| Mean (SD) | 1577.2 (316.6) | 1546.1 (258.6) |
| Median | 1534.0 | 1526.2 |
| Range | 456–2694 | 910–2450 |
| Number of infusion modifications, no. of patients (%) | | |
| 0 | 212 (97.2) | 109 (99.1) |
| 1 | 6 (2.8) | 1 (0.9) |

| | | |
|---|---|---|
| Number of infusion modifications due to an adverse event, no. of patients (%) | | |
| 0 | 212 (97.2) | 109 (99.1) |
| 1 | 6 (2.8) | 1 (0.9) |
| **Docetaxel** | | |
| Treatment duration, weeks | | |
| Mean (SD) | 12.0 (1.2) | 12.0 (0.7) |
| Median | 12.0 | 12.0 |
| Range | 3–16 | 6–14 |
| Number of cycles | | |
| Mean (SD) | 3.9 (0.4) | 4.0 (0.2) |
| Median | 4.0 | 4.0 |
| Range | 1–4 | 2–4 |
| Number of cycles, no. of patients (%) | | |
| 1 | 3 (1.4) | 0 |
| 2 | 1 (0.5) | 1 (0.9) |
| 3 | 0 | 1 (0.9) |
| 4 | 214 (98.2) | 108 (98.2) |
| Cumulative dose, mg | | |
| Mean (SD) | 479.2 (63.4) | 476.1 (47.0) |
| Median | 480.0 | 476.0 |
| Range | 116–612 | 258–626 |
| Number of dose modifications, no. of patients (%) | | |
| 0 | 207 (95.0) | 109 (99.1) |
| 1 | 10 (4.6) | 0 |
| 2 | 1 (0.5) | 1 (0.9) |
| Number of dose modifications due to an adverse event, no. of patients (%) | | |
| 0 | 210 (96.3) | 109 (99.1) |
| 1 | 8 (3.7) | 0 |
| 2 | 0 | 1 (0.9) |

SD, standard deviation.